

AMIFOSTINE - amifostine injection, powder, lyophilized, for solution
Sun Pharmaceutical Industries Limited

DESCRIPTION

Amifostine for injection is an organic thiophosphate cytoprotective agent known chemically as 2-[(3-aminopropyl) amino] ethanethiol dihydrogen phosphate (ester) and has the following structural formula:



Amifostine is a white crystalline powder, which is freely soluble in water. Its molecular formula is $\text{C}_5\text{H}_{15}\text{N}_2\text{O}_3\text{PS}$ and it has a molecular weight of 214.22.

Amifostine for Injection is the trihydrate form of amifostine and is supplied as a sterile powder requiring reconstitution for intravenous infusion. Each single-use 10 mL vial contains 500 mg of amifostine on the anhydrous basis.

CLINICAL PHARMACOLOGY

Amifostine is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite. This metabolite is believed to be responsible for the reduction of the cumulative renal toxicity of cisplatin. The ability of Amifostine to differentially protect normal tissues is attributed to the higher capillary alkaline phosphatase activity, higher pH and better vascularity of normal tissues relative to tumor tissue, which results in a more rapid generation of the active thiol metabolite as well as a higher rate constant for uptake into cells. The higher concentration of the thiol metabolite in normal tissues is available to bind to, and thereby detoxify, reactive metabolites of cisplatin. This thiol metabolite can also scavenge reactive oxygen species generated by exposure to cisplatin.

Pharmacokinetics:

Clinical pharmacokinetic studies show that Amifostine is rapidly cleared from the plasma with a distribution half-life of <1 minute and an elimination half-life of approximately 8 minutes. Less than 10% of Amifostine remains in the plasma 6 minutes after drug administration. Amifostine is rapidly metabolized to an active free thiol metabolite. A disulfide metabolite is produced subsequently and is less active than the free thiol. After a 10-second bolus dose of 150 mg/m^2 of Amifostine, renal excretion of the parent drug and its two metabolites was low during the hour following drug administration, averaging 0.69%, 2.64% and 2.22% of the administered dose for the parent, thiol and disulfide, respectively. Measurable levels of the free thiol metabolite have been found in bone marrow cells 5 to 8 minutes after intravenous infusion of Amifostine. Pretreatment with dexamethasone or metoclopramide has no effect on Amifostine pharmacokinetics.

Clinical Studies

Chemotherapy for Ovarian Cancer.

A randomized controlled trial compared six cycles of cyclophosphamide 1000 mg/m^2 , and cisplatin 100 mg/m^2 with or without Amifostine pretreatment at 910 mg/m^2 , in two successive cohorts of 121 patients with advanced ovarian cancer. In both cohorts, after multiple cycles of chemotherapy, pretreatment with Amifostine significantly reduced the cumulative renal toxicity associated with cisplatin as assessed by the proportion of patients who had $\geq 40\%$ decrease in creatinine clearance from pretreatment values, protracted elevations in serum creatinine ($>1.5 \text{ mg/dL}$), or severe hypomagnesemia. Subgroup analyses suggested that the effect of Amifostine was present in patients who had received nephrotoxic antibiotics, or who had preexisting diabetes or hypertension (and thus may have been at increased risk for significant nephrotoxicity), as well as in patients who lacked these risks. Selected analyses of the effects of Amifostine in reducing the cumulative renal toxicity of cisplatin in the randomized ovarian cancer study are provided in TABLES 1 and 2, below.

TABLE 1 Proportion of Patients with $\geq 40\%$ Reduction in Calculated Creatinine Clearance*

	Amifostine+CP	CP	p-value (2-sided)
All Patients	16/122 (13%)	36/120 (30%)	0.001
First Cohort	10/63	20/58	0.018
Second Cohort	6/59	16/62	0.026

*Creatinine clearance values were calculated using the Cockcroft-Gault formula, *Nephron* 1976; 16:31-41.

TABLE 2 NCI Toxicity Grades of Serum Magnesium Levels for Each Patient's Last Cycle of Therapy

NCI-CTC Grade: (mEq/L)	0 >1.4	1 ≤ 1.4 to >1.1	2 ≤ 1.1 to >0.8	3 ≤ 0.8 to >0.5	4 ≤ 0.5	p-value*
All Patients						
Amifostine+CP	92	13	3	0	0	0.001
CP	73	18	7	5	1	

First Cohort						
<u>Amifostine</u> +CP	49	10	3	0	0	0.017
CP	35	8	6	3	1	
Second Cohort						
<u>Amifostine</u> +CP	43	3	0	0	0	0.012
CP	38	10	1	2	0	

*Based on 2-sided Mantel-Haenszel Chi-Square statistic.

In the randomized ovarian cancer study, Amifostine had no detectable effect on the antitumor efficacy of cisplatin-cyclophosphamide chemotherapy. Objective response rates (including pathologically confirmed complete remission rates), time to progression, and survival duration were all similar in the Amifostine and control study groups. The table below summarizes the principal efficacy findings of the randomized ovarian cancer study.

TABLE 3 Comparison of Principal Efficacy Findings

	Amifostine +CP	CP
Complete pathologic tumor response rate	21.3%	15.8%
Time to progression (months)		
Median (± 95% CI)	15.8 (13.2, 25.1)	18.1 (12.5, 20.4)
Mean (± Std error)	19.8 (±1.04)	19.1 (±1.58)
Hazard ratio (95% Confidence Interval)	.98 (.64, 1.4)	
Survival (months)		
Median (± 95% CI)	31.3 (28.3, 38.2)	31.8 (26.3, 39.8)
Mean (± Std error)	33.7 (±2.03)	34.3 (±2.04)
Hazard ratio (95% Confidence Interval)	.97 (.69, 1.32)	

INDICATIONS AND USAGE

Amifostine for injection is indicated to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer.

For the approved indications, the clinical data do not suggest that the effectiveness of cisplatin based chemotherapy regimens is altered by Amifostine for injection. There are at present only limited data on the effects of Amifostine for injection on the efficacy of chemotherapy. Amifostine for injection should not be administered to patients in other settings where chemotherapy can produce a significant survival benefit except in the context of a clinical study (see WARNINGS).

CONTRAINDICATIONS

Amifostine for injection is contraindicated in patients with known hypersensitivity to aminothiols compounds.

WARNINGS

1. Effectiveness of the Cytotoxic Regimen

Limited data are currently available regarding the preservation of antitumor efficacy when Amifostine is administered prior to cisplatin therapy in settings other than advanced ovarian cancer. Although some animal data suggest interference is possible, in most tumor models the antitumor effects of chemotherapy are not altered by amifostine. Amifostine should not be used in patients receiving chemotherapy for other malignancies in which chemotherapy can produce a significant survival benefit or cure (e.g., certain malignancies of germ cell origin), except in the context of a clinical study.

2. Hypotension

Patients who are hypotensive or in a state of dehydration should not receive Amifostine. Patients receiving Amifostine at doses recommended for chemotherapy should have antihypertensive therapy interrupted 24 hours preceding administration of Amifostine. Patients receiving Amifostine at doses recommended for chemotherapy who are taking antihypertensive therapy that cannot be stopped for 24 hours preceding Amifostine treatment, should not receive Amifostine.

Prior to Amifostine infusion patients should be adequately hydrated. During Amifostine infusion patients should be kept in a supine position. Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated. It is important that the duration of the 910 mg/m² infusion not exceed 15 minutes, as administration of Amifostine as a longer infusion is associated with a higher incidence of side effects. For infusion durations less than 5 minutes, blood pressure should be monitored at least before and immediately after the infusion, and thereafter as clinically indicated. If hypotension occurs, patients should be placed in the Trendelenburg position and be given an infusion of normal saline using a separate i.v. line. During and after Amifostine infusion, care should be taken to monitor the blood pressure of patients whose antihypertensive medication has been interrupted since hypertension may be exacerbated by discontinuation of antihypertensive medication and other causes such as i.v. hydration.

Guidelines for interrupting and restarting Amifostine infusion if a decrease in systolic blood pressure should occur are provided in the DOSAGE AND ADMINISTRATION section. Hypotension may occur during or shortly after Amifostine infusion, despite adequate hydration and positioning of the patient (see ADVERSE REACTIONS and PRECAUTIONS). Hypotension has been reported to be associated with dyspnea, apnea, hypoxia, and in rare cases seizures, unconsciousness, respiratory arrest and renal failure.

3. Cutaneous Reactions

Serious cutaneous reactions have been associated with Amifostine administration. Serious cutaneous reactions have included erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, toxoderma and exfoliative dermatitis. These reactions have been reported more frequently when Amifostine is used as a radioprotectant (see ADVERSE REACTIONS). Some of these reactions have been fatal or have required hospitalization and/or discontinuance of therapy. Patients should be carefully monitored prior to, during and after Amifostine administration. Serious cutaneous reactions may develop weeks after initiation of Amifostine administration (see PRECAUTIONS).

4. Hypersensitivity

Allergic manifestations including anaphylaxis and severe cutaneous reactions have been associated with Amifostine administration. Nausea and Vomiting

Antiemetic medication should be administered prior to and in conjunction with Amifostine (see DOSAGE AND ADMINISTRATION). When Amifostine is administered with highly emetogenic chemotherapy, the fluid balance of the patient should be carefully monitored.

5. Hypocalcemia

Serum calcium levels should be monitored in patients at risk of hypocalcemia, such as those with nephrotic syndrome or patients receiving multiple doses of Amifostine (see ADVERSE REACTIONS). If necessary, calcium supplements can be administered.

PRECAUTIONS

General

Patients should be adequately hydrated prior to the Amifostine infusion and blood pressure should be monitored (see DOSAGE AND ADMINISTRATION).

The safety of Amifostine administration has not been established in elderly patients, or in patients with preexisting cardiovascular or cerebrovascular conditions such as ischemic heart disease, arrhythmias, congestive heart failure, or history of stroke or transient ischemic attacks. Amifostine should be used with particular care in these and other patients in whom the common Amifostine adverse effects of nausea/vomiting and hypotension may be more likely to have serious consequences.

Prior to chemotherapy, Amifostine should be administered as a 15-minute infusion (see DOSAGE AND ADMINISTRATION). Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated.

Cutaneous Reactions

Cutaneous reactions may require permanent discontinuation of Amifostine or urgent dermatologic consultation and biopsy (see below).

Cutaneous evaluation of the patient prior to each Amifostine administration should be performed with particular attention paid to the development of the following:

- Any rash involving the lips or involving mucosa not known to be due to another etiology (e.g., radiation mucositis, herpes simplex, etc.)
- Erythematous, edematous, or bullous lesions on the palms of the hands or soles of the feet and/or other cutaneous reactions on the trunk (front, back, abdomen)
- Cutaneous reactions with associated fever or other constitutional symptoms

Amifostine should be permanently discontinued for serious or severe cutaneous reactions (see WARNINGS and ADVERSE REACTIONS) or for cutaneous reactions associated with fever or other constitutional symptoms not known to be due to another etiology. Amifostine should be withheld and dermatologic consultation and biopsy considered for cutaneous reactions or mucosal lesions of unknown etiology appearing outside of the injection site and for erythematous, edematous or bullous lesions on the palms of the hand or soles of the feet. Reinitiation of Amifostine should be at the physician's discretion based on medical judgment and appropriate dermatologic evaluation.

Allergic Reactions

In case of severe acute allergic reactions Amifostine should be immediately and permanently discontinued. Epinephrine and other appropriate measures should be available for treatment of serious allergic events such as anaphylaxis.

Drug Interactions

Special consideration should be given to the administration of Amifostine in patients receiving antihypertensive medications or other drugs that could cause or potentiate hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate the carcinogenic potential of Amifostine. Amifostine was negative in the Ames test and in the mouse micronucleus test. The free thiol metabolite was positive in the Ames test with S9 microsomal fraction in the TA1535 *Salmonella typhimurium* strain and at the TK locus in the mouse L5178Y cell assay. The metabolite was negative in the mouse micronucleus test and negative for clastogenicity in human lymphocytes.

Pregnancy

Pregnancy Category C. Amifostine has been shown to be embryotoxic in rabbits at doses of 50 mg/kg, approximately sixty percent of the recommended dose in humans on a body surface area basis. There are no adequate and well-controlled studies in pregnant women. Amifostine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

No information is available on the excretion of Amifostine or its metabolites into human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, it is recommended that breast feeding be discontinued if the mother is treated with Amifostine.

Pediatric Use

The safety and effectiveness in pediatric patients have not been established.

Geriatric Use

The clinical studies did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in elderly patients.

ADVERSE REACTIONS

Controlled Trials

In the randomized study of patients with ovarian cancer given Amifostine at a dose of 910 mg/m² prior to chemotherapy, transient hypotension was observed in 62% of patients treated. The mean time of onset was 14 minutes into the 15-minute period of Amifostine infusion, and the mean duration was 6 minutes. In some cases, the infusion had to be prematurely terminated due to a more pronounced drop in systolic blood pressure. In general, the blood pressure returned to normal within 5 to 15 minutes. Fewer than 3% of patients discontinued Amifostine due to blood pressure reductions (see TABLE 4).

TABLE 4 Incidence of Common Adverse Events in Patients Receiving Amifostine

	Phase III Ovarian Cancer Trial (WR-1)	
	910 mg/m ² Per Patient	Per Infusion
Nausea/Vomiting		
≥Grade 3	36/122 (30%)	53/592 (9%)
All Grades	117/122 (96%)	520/592 (88%)
Hypotension		
≥Grade 3*	10/122 (8%)	
All Grades	75/122 (61%)	159/592 (27%)

*According to protocol-defined criteria. WR-1: requiring interruption of infusion; WR-38: drop of >20mm Hg.

Hypotension that requires interruption of the Amifostine infusion should be treated with fluid infusion and postural management of the patient (supine or Trendelenburg position). If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted, so that the full dose of Amifostine can be administered. Short term, reversible loss of consciousness has been reported rarely.

Nausea and/or vomiting occur frequently after Amifostine infusion and may be severe. In the ovarian cancer randomized study, the incidence of severe nausea/vomiting on day 1 of cyclophosphamide-cisplatin chemotherapy was 10% in patients who did not receive Amifostine, and 19% in patients who did receive Amifostine.

Decrease in serum calcium concentrations is a known pharmacological effect of Amifostine. At the recommended doses, clinically significant hypocalcemia was not reported in the ovarian cancer study.

Other effects, which have been described during, or following Amifostine infusion are flushing/feeling of warmth, chills/feeling of coldness, malaise, fever, rash, dizziness, somnolence, hiccups and sneezing. These effects have not generally precluded the completion of therapy.

Clinical Trials and Pharmacovigilance Reports

Allergic reactions characterized by one or more of the following manifestations have been observed during or after Amifostine administration: hypotension, fever, chills/rigors, dyspnea, hypoxia, chest tightness, cutaneous eruptions, pruritus, urticaria and laryngeal edema. Cutaneous eruptions have been commonly reported during clinical trials and were generally non-serious. Serious, sometimes fatal skin reactions including erythema multiforme, and in rare cases, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis have also occurred. Rare anaphylactoid reactions and cardiac arrest have also been reported. Hypotension, usually brief systolic and diastolic, has been associated with one or more of the following adverse events: apnea, dyspnea, hypoxia, tachycardia, bradycardia, extrasystoles, chest pain, myocardial ischemia and convulsion. Rare cases of renal failure, myocardial infarction, respiratory and cardiac arrest have been observed during or after hypotension. (See WARNINGS and PRECAUTIONS)

Rare cases of arrhythmias such as atrial fibrillation/flutter and supraventricular tachycardia have been reported. These are sometimes associated with hypotension or allergic reactions.

Transient hypertension and exacerbations of preexisting hypertension have been observed rarely after Amifostine administration. Seizures and syncope have been reported rarely. (See WARNINGS and PRECAUTIONS)

OVERDOSAGE

In clinical trials, the maximum single dose of Amifostine was 1300 mg/m². No information is available on single doses higher than this in adults. In the setting of a clinical trial, pediatric patients have received single Amifostine doses of up to 2700 mg/m². At the higher doses, anxiety and reversible urinary retention occurred.

Administration of Amifostine at 2 and 4 hours after the initial dose has not led to increased nausea and vomiting or hypotension.

The most likely symptom of overdosage is hypotension, which should be managed by infusion of normal saline and other supportive measures, as clinically indicated.

DOSAGE AND ADMINISTRATION

For Reduction of Cumulative Renal Toxicity with Chemotherapy: The recommended starting dose of Amifostine for injection is 910 mg/m² administered once daily as a 15-minute i.v. infusion, starting 30 minutes prior to chemotherapy.

The 15-minute infusion is better tolerated than more extended infusions. Further reductions in infusion times for chemotherapy regimens have not been systematically investigated.

Patients should be adequately hydrated prior to Amifostine for injection infusion and kept in a supine position during the infusion.

Blood pressure should be monitored every 5 minutes during the infusion, and thereafter as clinically indicated.

The infusion of Amifostine for injection should be interrupted if the systolic blood pressure decreases significantly from the baseline value as listed in the guideline below:

Guideline for Interrupting Amifostine for injection Infusion Due to Decrease in Systolic Blood Pressure

	Baseline Systolic Blood Pressure (mm Hg)				
	<100	100 to 119	120 to 139	140 to 179	≥180
Decrease in systolic blood pressure during infusion of Amifostine for injection (mm Hg)	20	25	30	40	50

If the blood pressure returns to normal within 5 minutes and the patient is asymptomatic, the infusion may be restarted so that the full dose of Amifostine for injection may be administered. If the full dose of Amifostine for injection cannot be administered, the dose of Amifostine for injection for subsequent chemotherapy cycles should be 740 mg/m².

It is recommended that antiemetic medication, including dexamethasone 20 mg i.v. and a serotonin 5HT₃ receptor antagonist, be administered prior to and in conjunction with Amifostine for injection. Additional antiemetics may be required based on the chemotherapy drugs administered.

Reconstitution

Amifostine for Injection is supplied as a sterile powder requiring reconstitution for intravenous infusion. Each single-use vial contains 500 mg of amifostine on the anhydrous basis.

Prior to intravenous injection, Amifostine for injection is reconstituted with 9.7 mL of sterile 0.9% Sodium Chloride Injection, USP. The reconstituted solution (500 mg amifostine/10 mL) is chemically stable for up to 5 hours at room temperature (approximately 25°C) or up to 24 hours under refrigeration (2°C to 8°C).

Amifostine for injection prepared in polyvinylchloride (PVC) bags at concentrations ranging from 5 mg/mL to 40 mg/mL is chemically stable for up to 5 hours when stored at room temperature (approximately 25°C) or up to 24 hours when stored under refrigeration (2°C to 8°C). CAUTION: Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if cloudiness or precipitate is observed.

Incompatibilities

The compatibility of Amifostine for injection with solutions other than 0.9% Sodium Chloride for Injection, or Sodium Chloride solutions with other additives, has not been examined. The use of other solutions is not recommended.

HOW SUPPLIED

Amifostine for Injection USP is supplied as a sterile powder in 10 mL single-use vials (NDC 62756-581-40). Each single-use vial contains 500 mg of amifostine on the anhydrous basis. The vials are available packaged as follows:

1 pack - 1 vial per carton (NDC 62756-581-40).

3 pack - 3 vials per carton (NDC 62756-581-42).

Store the powder dosage form at Controlled Room Temperature 20°-25°C (68°-77°F) [See USP].

Distributed by:

Caraco Pharmaceutical Laboratories, Ltd.

1150 Elijah McCoy Drive, Detroit, MI 48202

Manufactured by:

Sun Pharmaceutical Ind. Ltd.

Acme Plaza, Andheri-Kurla Road,

Andheri (East), Mumbai -400 059, India.

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PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - VIAL LABEL

NDC 62756-581-40

Amifostine for Injection USP

500 mg/vial

Sterile

Single use vials

For Intravenous Use

Rx only



PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - SHOWBOX FOR 1 VIAL

NDC 62756-581-40

Amifostine for Injection USP

500 mg/vial

Sterile




Single use vials

For Intravenous Use

1 Vial

Rx only

Sun Pharmaceutical Industries Ltd.

<p>For Intravenous Use Single use vials Sterile</p> <p>Amifostine for Injection USP 500 mg/vial</p> <p>NDC 62756-581-40</p>			
<p>Amifostine for Injection USP Each single use vial contains: 500 mg amifostine (anhydrous basis) Must be diluted prior to I.V. use Usual Dosage: See package insert for dosage information. Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]. When reconstituted with 9.7 mL of 0.9% Sodium Chloride Injection, USP each milliliter will contain 50 mg of amifostine. Contains no preservatives. Reconstituted solutions should be used within five hours when stored at room temperature (approximately 25°C). Distributed by:  CARACO Pharmaceuticals, Inc. Bridgewater, NJ 08807 Manufactured by: Sun Pharmaceutical Ind. Ltd. Acme Plaza, Andheri-Kurla Road, Andheri (East), Mumbai-400 059, India.</p>	<p>NDC 62756-581-40</p> <p>Amifostine for Injection USP 500 mg/vial</p> <p>Sterile Single use vials For Intravenous Use</p> <p>PJS80487 PJS80487 ISS: 10/2007</p> <p>GUJ/DRUGS/28/396 Batch No.: Exp.:</p>	<p>NDC 62756-581-40</p> <p>Amifostine for Injection USP 500 mg/vial</p> <p>Sterile Single use vials For Intravenous Use</p> <p>1 Vial Rx only</p> 	<p>NDC 62756-581-40</p> <p>Amifostine for Injection USP 500 mg/vial</p> <p>Sterile Single use vials For Intravenous Use</p>  N 62756 581 40 1

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - SHOWBOX FOR 3 VIALS

NDC 62756-581-42

Amifostine for Injection USP

500 mg/vial

Sterile

Single use vials

For Intravenous Use

3 Vials

Rx only

Sun Pharmaceutical Industries Ltd.

NDC 62756-581-42

Amifostine for Injection USP

500 mg/vial

Sterile
Single use vials
For Intravenous Use

3 Vials
Rx only



Amifostine for Injection USP

CAUTION: US 28306
Batch No.:
Exp.:

Manufactured by:
Sun Pharmaceutical Ind., Ltd.
Acme Plaza, Andheri-Kurla Road,
Andheri (East), Mumbai-400 099, India.



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1 62756 581 42

NDC 62756-581-42

Amifostine for Injection USP

500 mg/vial

Sterile
Single use vials
For Intravenous Use

3 Vials
Rx only



NDC 62756-581-42
Amifostine for Injection USP

500 mg/vial
Sterile
Single use vials
For Intravenous Use
3 Vials
Rx only

NDC 62756-581-42
Amifostine for Injection USP
500 mg/Vial
Sterile
Single use vials
For Intravenous Use
3 Vials
Rx only

Amifostine for Injection USP

Each single use vial contains:
500 mg amifostine (anhydrous basis)
Must be diluted prior to IV use.

Usual Dosage: See package insert for dosage information.

Store at 20-25°C (68°-77°F) [see USP Controlled Room Temperature]. When reconstituted with 0.7 mL of 0.9% Sodium Chloride Injection, USP each milliliter will contain 50 mg of amifostine. Contains no preservatives. Reconstituted solutions should be used within five hours when stored at room temperature (approximately 25°C).